Section 4)

Attachment no. 3

LSR-RTC S.p.A.:

Chronic Toxicity of Fructose-1,6-Diphosphate,

1991

VOL. I

RPT188

LIFE SCIENCE RESEARCH
ROMA TOXICOLOGY CENTRE S.P.A.

FDP
13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

LSR-RTC Study No.: 235-003-009

LSR-RTC Report No.: 235-003-009/T/080/90

FINAL REPORT

CONFIDENTIAL

Seen and approved by:

A. Nunziata
Responsible for Toxicological Experimentation as authorized by the Italian Ministry of Health

Dr. R. K. Haroz
Managing Director

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FINAL REPORT

We, the undersigned, hereby declare that this report provides a correct and faithful record of the procedures adopted and the results obtained in the performance of this study.

Marianne Eileraas 14-5-91
M. Eileraas, Pharm. D.
(Study Director)

M. F. Mariani 14-5-91
M. F. Mariani, M. D., Ph. D.
(Head, General Toxicology)

14.5.91
A. Argentino-Storino, Biol. D., Spec. Gen. Path.
(Pathologist)

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Roma Toxicology Center S.p.A.
(Dr. Alfredo [illegible])

LSR-RTC Report No.: 235-003-009/T/080/90

COMPLIANCE STATEMENT

We, the undersigned, hereby declare that the following report constitutes a true and faithful account of the procedures adopted, and the results obtained in the performance of this study. The aspects of the study conducted by Life Science Research - Roma Toxicology Centre were performed essentially in accordance with:

A. "Good Laboratory Practice" regulations of the U.S. Food and Drug Administration, 21 CFR Part 58, 22 December 1978 and sections revised in Fed. Reg. 4 September 1987.

B. "Principles of Good Laboratory Practice relating to the conduct of Non-Clinical Laboratory Studies" OECD Guidelines for the testing of Chemicals, Annex 2, (81) 30 (Final) 1981.

C. "Applicazione dei principi di buone pratiche di laboratorio sulle sostanze chimiche e criteri per il rilascio delle autorizzazioni previste dal decreto del Presidente della Repubblica no. 927/81, art.6." Roma, Italy, D.M. no. 76 Gazzetta Ufficiale del 27 Agosto 1986.

Study Director : Marianne Eileraas Date : 14-5-91
(M.Eileraas, Pharm.D.)

Head of Department : J. Brightwell Date : 14.05.91
(J. Brightwell, Ph.D.)

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(Dr. Alfredo Nunziata)

LSR-RTC Report No.: 235-003-009/T/080/90

Q.A. STATEMENT

	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROTOCOL			
Inspections of the study protocol and protocol amendment were made in accordance with LSR-RTC Standard Operating Procedure QAU/010.	03.11.89 03.01.90	03.11.89 04.01.90	03.11.89 04.01.90
DATA			
Inspections of data generated on this type of study were made in accordance with LSR-RTC Standard Operating Procedure QAU/030.	04.01.90 04.01.90 17.10.89	--------- --------- ---------	04.01.90 04.01.90 23.10.89
PROCEDURES			
Inspections of Procedures on this study were made in accordance with LSR-RTC Standard Operating Procedure QAU/020.	14.11.89 17.11.89 28.11.89 29.11.89 30.11.89 19.12.89 19.12.89 22.12.89 05.01.90 08.01.90 10.01.90 28.02.90 28.02.90	17.11.89 28.11.89 01.12.89 22.12.89 19.01.90 09.01.90 09.01.90 09.01.90 24.01.90 24.01.90 26.04.90 13.03.90 06.04.90	17.11.89 28.11.89 01.12.89 22.12.89 19.01.90 09.01.90 09.01.90 09.01.90 24.01.90 24.01.90 26.04.90 13.03.90 06.04.90

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Q.A. STATEMENT

	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROCEDURES (continued)			
Other routine procedures performed in this type of study, and facilities were inspected regulary and reports were made in accordance with LSR-RTC Standard Operating Procedure QAU/020.	04.09.89	---------	07.09.89
	16.10.89	---------	17.10.89
	03.11.89	---------	29.11.89
	14.11.89	---------	17.11.89
	21.11.89	---------	22.11.89
	06.12.89	---------	07.12.89
	06.12.89	---------	07.12.89
	14.12.89	---------	14.12.89
	14.12.89	---------	14.12.89
	03.01.90	---------	19.01.90
	08.02.90	---------	09.02.90
	12.02.90	---------	15.02.90
	19.03.90	---------	20.03.90
	22.03.90	---------	27.03.90
	26.03.90	---------	27.03.90
	13.04.90	---------	16.05.90
	18.04.90	---------	11.05.90
	22.05.90	---------	31.05.90
	12.06.90	---------	15.06.90

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(Dr. Alfredo Nanziata)

This report has been reviewed by the LSR-RTC Quality Assurance Unit employing methods laid down in LSR-RTC Standard Operating Procedure QAU/040. The reported methods and procedures were found to describe those used and the results to constitute an accurate representation of the data recorded.

This review was completed on: 14th May, 1991

V. Sforza, B.Sc.
(Quality Assurance Manager) 14/05/91

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ADDENDA

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(Dr. Alfredo Nunziata)

1. SUMMARY

1.1 The intravenous toxicity of Fructose-1,6-diphosphate (FDP), when administered daily to dogs over a period of 13 weeks has been investigated. Three groups of 4 male and 4 female beagle dogs received Fructose-1,6-diphosphate (FDP) via the left and right cephalic and right saphenous veins used in rotation at dosages of 110, 220 and 440 mg/kg/day, while a fourth, similarly constituted group, received the vehicle (isotonic saline) and acted as a control.

1.2 Signs of possible toxicological significance such as increased activity and/or tremor, reddening of the external epithelia (eyes, gums and ears), and licking lips were mainly seen in animals in the high dose group (440 mg/kg/day) and occasionally in the mid dose group (220 mg/kg/day). Additional reactions to administration of FDP to dogs consisted of isolated episodes of emesis, salivation and, possibly, mandibular ptosis (described as mouth open), which were mainly seen in animals in the high dose group.
Except for an apparently dosage related increase in heart rate and for isolated episodes of vocalization, occurring in all but the low dose female group, no clear signs of adverse reactions were evidenced in animals receiving 110 mg/kg/day.

1.3 Slightly lower than control mean body weight was observed throughout the study for high dose animals of both sexes (440 mg/kg/day).

1.4 Food intake of the treated groups remained comparable to that of the controls.

1.5 No consistent differences in water consumption were observed at the measurements performed during the study.

1.6 The electrocardiography performed during weeks 1 and 12 of the study did not show any changes that could be related to treatment.

1.7 No treatment related abnormalities were observed at the physical examination performed during the study.

1.8 The ophthalmoscopic examinations performed during treatment did not reveal any evidence of treatment related changes.

1.9 There were no changes in the haematological parameters which could be confidently attributed to treatment with FDP.

1.10 No relevant changes were seen at the clinical chemistry measurements taken at weeks 6 and 13 of the study.

1.11 No treatment related changes were measured at the urinalysis and faecal analysis performed at weeks 6 and 13 of study.

1.12 Relative kidney weights statistically significant lower than controls were observed for mid- (220 mg/kg/day) and high-dose (440 mg/kg/day) females. Mean relative heart (both sexes) and spleen (females) weights of treated animals were also slightly increased.

1.13 Areas of abnormal colour were detected on the mucosal surface of the intestine of one male and one female receiving 220 mg/kg/day and one female receiving 440 mg/kg/day. An increased incidence of dark contents was observed in the gall bladder of mid and high dose males, only.

1.14 Mucosal congestion of the intestine of doubtful toxicological significance was observed in one low-dose (110 mg/kg/day) male, in one male and one female receiving 220 mg/kg/day and in one male and one female receiving 440 mg/kg/day. An isolated instance of congestion of the mucosal surface was detected in the gall bladder of one male in the high dose group. One instance of kidney tubular dilatation was found in a second high dose male.

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2. INTRODUCTION

The purpose of this study was to evaluate the toxicity of FDP when administered by daily intravenous injection in a 13 week study in dogs. The Beagle dog was chosen because it is a requirement of many regulatory authorities and because there is an accumulation of experience and background data on this species. The intravenous route was selected as it is one of the therapeutic routes of administration of the test substance in man. The dosage levels of 110, 220 and 440 mg/kg/day were chosen in consultation with the Client and were based on the information from a preliminary study carried out at LSR-RTC (LSR-RTC Report No.: 229-0-003-007/T/071/89).

The study was performed at:

Life Science Research - Roma Toxicology Centre
Via Tito Speri, 12
00040 Pomezia
Roma
Italy

The electrocardiographic evaluation was performed by:

Prof. G. Zannetti
(Consultant cardiologist)
Universita' degli Studi di Parma
Facolta' di Medicina Veterinaria
Istituto di Clinica Medica Veterinaria
Via del Taglio
Cornocchio
43100 Parma
Italy

The animals were allocated to treatment groups on 14-11-1989.
Dosing commenced on 28-11-1989 and the necropsy was performed from 27-2-1990 to 1-3-1990.
The protocol and protocol amendment are presented in Addendum V.

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3. TEST SUBSTANCE

1900 vials, each containing 5 g of FDP (Fructose-1-6-diphosphate), batch no. 521 B, were received on 18.10.89. The test substance, a pale yellow powder, was stored within the Formulation Unit at ambient temperature, protected from light.

The identity, strength, purity, composition and stability of the test substance were the responsibility of the Client.

Samples of the test substance were taken before the commencement of treatment and after completion of the treatment period and stored in the archives at LSR-RTC. These samples will be retained at LSR-RTC for 5 years. An additional sample was taken on completion of the treatment period and sent to the Client for analysis. The certificate of analysis of the test substance is presented in Addendum II.

4. METHODS

4.1 Animal management

4.1.1 Animal supply and acclimatization

A total of 36 pure-bred Beagle dogs (18 males and 18 females), approximately 23-26 weeks of age and with a weight range of 6.58-9.34 kg for the males and 6.14-8.36 kg for the females, were supplied by Allevamento Soprani, S. Polo D'Enza, Reggio Emilia, Italy. The dogs were selected at the supplier's premises by an LSR-RTC veterinary surgeon to ensure that the animals were suitable for use on study. All dogs were vaccinated by the supplier against hepatitis, leptospirosis and distemper (Candur CEL, Behringwerke) at approximately 8 and 12 weeks of age. Before delivery to LSR-RTC, all dogs were vaccinated against rabies (Dohyvac i-R, From Laboratories, Wisconsin, USA) and Parvovirus.
On arrival each dog was assigned a unique animal number which was tattooed on the ear and stamped on a metal disc attached to a collar around the dog's neck. Even numbers were assigned to males, odd to females. An acclimatization period of 25 days was allowed before the start of treatment.

4.1.2 Health check

As soon as possible after arrival each animal was subjected to a detailed examination by a veterinary surgeon to ensure it was in a good state of health. An antiparasitic (LEN, Teknofarma) was also given shortly after arrival and this treatment was repeated twice at 1 day intervals; a second course of treatment was administered approximately 20 days later.

Blood samples were obtained from the jugular vein of each dog for haematological and biochemical screening (see section 4.4). Overnight urine samples were also collected.

4.1.3 Animal husbandry

The animals were housed inside a limited access dog facility. Temperature and humidity were monitored daily and these data are retained in archives. A standby power supply was automatically brought into operation if the public electricity supply failed. Personnel entering the facility were required to wear protective clothing. On entry to animal rooms additional protective clothing was worn dependent upon the Hazard Classification assigned to the test substance.
Dogs were individually housed, in indoor kennels of approximately 0.9 x 1.0m floor area with an attached individual open air pen.
Sawdust used as bedding was changed daily. During this period dogs were exercised in the kennel area or confined to the open air pen.

4.1.4 Water diet and sawdust supply

Drinking water was supplied ad libitum to each kennel via an automatic "lixit" valve system or water bottles, except when urine was collected. Each dog was offered 400 g daily of a complete pelleted dog diet (Altromin H, A. Rieper, Bolzano) at least half an hour prior to dosing. There was no information available to indicate that any non-nutrient substance likely to influence the effect of the test substance was present in the drinking water, diet or sawdust bedding material.
Records of analysis of diet, water and sawdust are kept on file at LSR-RTC.

4.1.5 Allocation to groups

On the day of allocation (11 days after arrival at LSR-RTC) all the dogs were weighed and temporarily allocated to groups by computerized stratified randomization to give approximately equal initial group mean body weights. Thereafter, pre-treatment investigations were carried out on all dogs from the batch supplied for the study, including dogs designated as spare animals in the allocation process described above. Shortly before the start of treatment, on the 27th November 1989, the allocation was reviewed on the basis of pre-treatment clinical pathology investigations, as follows:
- Animal no. 1772, originally allocated as 2350018, was exchanged with spare dog no. 1776.
- Animal no. 1723, originally allocated as 2350009, was exchanged with spare dog no. 1745.

From allocation, each kennel was identified by a label, colour-coded according to group as detailed below (Section 4.2.1) and recording the study number, animal number and details of treatment. The colour-coding matched the appropriate colour-coded formulation container.
The animal allocation to kennels was selected to minimize, as far as possible, any environmental effects (see Figure 1).

4.2 Treatment

4.2.1 Treatment, group sizes and identification

Each group comprised 4 male and 4 female dogs. The group identification and animal numbers of animals assigned to the treatment are summarised below:

Group: Colour code	Treatment (mg/kg/day)+	Concentration (mg/ml)+	Dog numbers M (even)	Dog numbers F (odd)
1: white	0	0	2-8	1-7
2: yellow	110	55	10-16	9-15
3: blue	220	110	18-24	17-23
4: red	440	220	26-32	25-31

+ In terms of Fructose-1,6-diphosphate dehydrated sodium salt (FDP Na_3H).

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The study and animal number for each dog were stamped on a metal disc attached to a chain collar secured around the dog's neck.

4.2.2 Method and frequency of dose preparation

For the highest concentration of 220 mg/ml the required amount of test substance was dissolved in isotonic saline and sterilized by Millipore filtration (0.2 micrometres). The lower concentrations of 110 mg/ml and 55 mg/ml were prepared by serial dilution of the highest concentration with isotonic saline. The solutions were prepared daily. The dosage volume required for daily administration was calculated in advance based on the most recently recorded body weight.
Samples of the formulations prepared for all treatment groups were taken in weeks 1 and 13, deep frozen and sent to the Client for analysis. The results of these analyses which are presented in Addendum III, were considered satisfactory.

4.2.3 Administration of test substance

The test substance was administered intravenously, at an approximate rate of 5-8 ml/min, via the left and right cephalic and right saphenous veins, used in rotation (the left saphenous veins acted as a within animal control), at least half an hour after feeding. The dose was administered to each animal on the basis of the most recently recorded body weight at a dose volume of 2 ml/kg body weight.

4.2.4 Duration of treatment

All animals were dosed once daily for 13 consecutive weeks and up until the day before necropsy.

4.3 In vivo observations

Dated and signed records of all activities relating to the day by day running and maintenance of the study within the animal unit, as well as to the group observations and examinations were recorded in the Study Day Book.

4.3.1 Clinical signs

All clinical signs were recorded for individual animals. Daily records of the kennels were also maintained (for vomitus, blood, diarrhoea etc.). Once per treatment week, and wherever possible at seven day intervals, each animal was subjected to an additional physical examination and any clinical sign was recorded. Dated and signed records of appearance and change of clinical signs were maintained on clinical history sheets for individual animals.

4.3.2 Mortality

Throughout the study, all pens were checked early in each working day and again in the afternoon to look for dead or moribund animals. At weekends and Public Holidays a similar procedure was followed except that the final check was carried out at approximately mid-day.

4.3.3 Body weight

The dogs were weighed three times during the first week after arrival and at weekly intervals during the remainder of the acclimatization period. During the treatment period all dogs were weighed twice weekly up to week 4 and weekly thereafter. All dogs were weighed prior to necropsy. All weighings were performed before feeding.

4.3.4 Food consumption

The weight of food consumed by each dog was recorded daily.

4.3.5 Water consumption

Measurements of the the water consumed by each animal were performed over 3 day periods twice during the pre-treatment period and over a 3 day period during weeks 1, 7 and 13.

4.3.6 Veterinary examination

Each animal was subjected to an examination by a veterinary officer before dosing commenced and thereafter at approximately monthly intervals in which particular attention was paid to:

Teeth and gums
Mucous membranes and skin
Ears (external auditory canal)
Superficial lymph-nodes
Abdomen - including palpation
External genitalia and mammary glands
Chest - including auscultation of heart and lungs
Stance - including palpation of limbs
General behaviour and appearance

The outcome of this examination was recorded for every animal.

4.3.7 Ophthalmoscopy

Both eyes of all animals assigned to the study were examined just prior to the commencement of treatment by means of an ophthalmoscope approximately 20 minutes after the instillation of 1% Tropicamide (Visumidriatic, MSD). The eyes of all animals in all groups were re-examined during weeks 6 and 12.

4.3.8 Electrocardiography

Once before treatment comenced electrocardiography tracings were recorded for all dogs using the three standard limbs leads (I, II and III) and the three augmented limb leads (aVR, aVL and aVF). During weeks 1 and 12 further tracings were obtained, just prior to and after administration (where possible within 15 minutes after dosing). From the tracings obtained the following were measured:

Heart rate
Wave intervals
Amplitude
The R/T ratio was calculated from the amplitude measurement

4.4 Clinical pathology evaluation

Twice before commencement of treatment and during weeks 6 and 13 samples of blood were withdrawn from the jugular vein of each dog after overnight fasting. Once before commencement of treatment and during weeks 6 and 13 individual overnight urine samples were collected from all dogs under conditions of food and water deprivation and faecal samples were also collected from metabolism cage or from the pen. The blood samples collected were divided into tubes as follows:

EDTA anticoagulant . . . . . for haematological investigations
Citrate anticoagulant . . . . . for coagulation tests
No anticoagulant . . . . . for the biochemical tests

The estimations performed on blood and urine samples are listed below:

4.4.1 Haematology

Erythrocyte sedimentation rate
Packed cell volume
Haemoglobin concentration
Erythocyte count
Reticulocyte count (if there were signs of anaemia)
Mean cell haemoglobin
Mean cell volume
Mean cell haemoglobin concentration
Total leucocyte count
Differential leucocyte count - Neutrophils
- Lymphocytes
- Eosinophils
- Basophils
- Monocytes
Abnormalities of the blood film
Platelet count
Prothrombin time
Partial thromboplastin time

4.4.2 Clinical chemistry

Alkaline phosphatase
Alanine amino-transferase
Aspartate amino-transferase
Urea
Creatinine
Glucose
Bilirubin
Cholesterol
Total protein
Protein electrophoretogram - Albumin
- Alpha-one globulin
- Alpha-two globulin
- Beta globulin
- Gamma globulin
- Albumin/globulin ratio
Sodium
Potassium
Calcium
Chloride

4.4.3 Urinalysis

Appearance
Volume
Specific gravity
pH
Protein
Total reducing substances
Glucose
Ketones
Bilirubin
Urobilinogen
Nitrite
Blood

The sediment, obtained from centrifugation at approximately 3000 r.p.m. for 10 minutes, was examined microscopically for

Epithelial cells
Polymorphonuclear leucocytes
Erythrocytes
Crystals
Spermatozoa and precursors
Other abnormal components

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4.4.4 Faecal analysis

Feacal occult blood

4.5 Terminal studies

4.5.1 Euthanasia

After completion of the scheduled test period all animals were placed under intravenous barbiturate anaesthesia and killed by rapid exsanguination. All animals were subjected to necropsy, supervised by a pathologist, as detailed below.

4.5.2 Bone marrow

During the necropsy procedure bone marrow samples were obtained from a rib from all animals. Smears prepared from these samples were air dried, fixed in methanol and stained using a May-Grunwald-Giemsa procedure. The smears were examined for abnormalities and the myeloid/erythroid ratio calculated.

4.5.3 Necropsy procedure

The clinical history of the animal was studied and a detailed post mortem examination was conducted (including examination of the external surface and orifices). Changes were noted, the requisite organs weighed and the required tissue samples preserved in fixative (see sections 4.5.4, 4.5.5).

4.5.4 Organ weights

The following organs from all animals completing the scheduled test period were dissected free of fat and weighed:

Adrenal glands	Pituitary gland
Brain	Spleen
Heart	Testes
Kidneys	Thyroid and parathyroid glands
Liver	Uterus
Ovaries	

The ratios of organ weight to body weight were calculated for each animal.

4.5.5 Tissues preserved in fixative

Samples of all the tissues listed below were preserved in 10% buffered formol-saline (except eyes and optic nerves which were preserved in Davidson's fixative).

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Abnormalities
Adrenal glands
Aorta
Bone marrow (from sternum)
Brain
Bronchi
Caecum
*Cervix
Colon
Duodenum
Epididymides
Eyes
*Femur (including articular surface)
Gall bladder
Heart
Ileum
Injection site (s)
Jejunum
Kidneys
*Larynx
Liver
Lungs
Lymph nodes-Submandibolar
Lymph nodes-Mesentric
Lymph nodes-Peribronchial
Mammary area
Nictitating membranes
Nictitating glands
Oesophagus
Optic nerves
Ovaries
Pancreas
Parathyroid glands
*Pharynx
Pituitary gland
Prostate gland
Rectum
Salivary gland
Sciatic nerve
Skeletal muscle
Skin
Spinal cord
Spleen
Sternum
Stomach
Testes
Thymus (were present)
Thyroid gland
Tongue
Trachea
Urinary bladder
Uterus
*Vagina

* These tissues were preserved but not processed further.

4.5.6 Histopathology examination

The tissues required for histopathological examination are listed above. After dehydration and embedding in paraffin wax, sections of the tissues were cut at 5 micrometres thickness and stained with haematoxylin and eosin. The tissues specified above from all animals in all dosage groups were examined.

4.5.7 Photomicrography

No photomicrographs were taken.

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4.6 Statistical analysis

Standard deviations were calculated as considered appropriate. For continuous variables the significance of the differences amongst groups was assessed by analysis of variance. Differences between each treated group and the control group were assessed by Dunnett's Test using a pooled error variance. The mean values, standard deviations and statistical analysis are calculated from the actual values in the computer without rounding off.
In the case of biochemical data and organ weight the homogeneity was verified by Bartlett's Test before Dunnett's T test was performed. If the data were not found homogeneous a Modified T Test (Cockran and Cooks) was applied. Microscopic observations were tested for statistical significance using the non-parametric Kolmogorov-Smirnov test.

4.7 Deviations from protocol

Instead of a weight range of 5-7.5 kg, as stated by the protocol, the animals weighed, at arrival, 6.58-9.34 kg for the males and 6.14-8.36 for the females. The animals were 23-26 weeks of age, instead of approximately 20 weeks of age.
According to the protocol, measurements of water consumption should have been performed during week 6. Instead, the measurement of water consumption was performed during week 7.
Urine collection was performed during week 6 instead of week 5, as stated by the protocol.
Due to a change in the computer system data management at LSR-RTC, the tables of Haematology and Clinical Chemistry have some different parameter names compared to the protocol list of parameters:

Packed cell volume	Haematocrit
Haemoglobin concentration	Haemoglobin
Erythrocyte count	Red blood cell count
Mean cell haemoglobin	Mean corpuscular haemoglobin
Mean cell volume	Mean RBC cell volume
Mean cell haemoglobin concentration	Mean corpuscular Hb conc.
Total leucocyte count	White blood cell count
Platelet count	Platelets
Alanine amino-transferase	Alanine transferase
Aspartate amino-transferase	Aspartate transferase
Cholesterol	Total cholesterol
Bilirubin	Total bilirubin

These deviations from the protocol are not considered to affect the integrity of the study.

There were no other deviations from the protocol which are considered to have affected the integrity of the study.

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4.8 Archives

All samples of tissues, raw data, records and documentation generated during the course of this study will be retained at LSR-RTC for a period of at least five years. The data will not be destroyed without the consent of the Sponsor.

5. RESULTS AND DISCUSSION

5.1 Clinical signs (Table 1)

Intravenous administration of FDP was associated with tremors and/or increased activity, reddening of external epithelia (limited to eyes, gums and ears) and licking lips which were almost exclusively observed in animals receiving 440 and, to a lesser extent, 220 mg/kg/day. These signs, usually observed during administration, were in general not evident at 60 to 120 minutes. Additional signs of likely toxicological significance such as emesis, an overall increased incidence in salivation and opening of the mouth, possible indication of mandibular ptosis, were exclusively limited to animals receiving 440 mg/kg/day.
No clinical signs of clear toxicological significance were observed in animals receiving 110 mg/kg/day. Although an apparently dosage related increase in heart rate as well as isolated episodes of vocalization (the latter sign not observed in low dose females, but marked in high dose dogs) were evidenced in animals at all dosages tested, the relatively low incidence of the above signs and the nature of the route of administration make the toxicological significance of these signs doubtful.
The remaining signs(e.g. hairloss, excoriation, erythema, ocular discharge, lachrymation, damaged tail) observed were seen in animals from all groups, control group included, and were without significance.

5.2 Body weight (Figure 2; Table 2; Appendix 1)

The mean body weights of animals from both sexes receiving 440 mg/kg/day remained slightly lower than that of the control group throughout the study. The differences observed for the remaining groups were either marginal or were evident in only one sex and have no toxicological significance.

5.3 Food consumption (Table 3; Appendix 2)

There were no intergroup differences in food consumption which could be ascribed to treatment with FDP.

5.4 Water consumption (Table 4; Appendix 3)

The changes in water consumption occurring during the study were not consistent. The statistically significant differences observed on occasions should be considered as incidental and not related to test substance administration.

5.5 Electrocardiography (Addendum IV)

A general evaluation of the electrocardiographic analysis showed no significant changes on the traces for any group or phase of the study. Any changed observed were considered to be attributed to physiological conditions of myocard "maturation" processes that are completely normal in animals in the final phases of somatic development.

5.6 Veterinary examination (Table 5; Appendix 4)

Apart from increased heart rate observed on one occasion during the administration of the test substance, the veterinary examinations performed during the study did not identify any abnormalities that could definitely be attributed to treatment.

5.7 Ophthalmoscopy (Table 6)

No treatment related changes were observed at the ophthalmoscopic examinations performed during the study.

5.8 Haematology (Table 7; Appendix 5)

Apparent differences in the haematological measurements performed at weeks 6 and 13 of study were observed. However, although reaching statistical significance on occasions, none of them could be confidently attributed to treatment as similar differences between treatment and control groups were already evident before the start of the treatment period.

5.9 Bone marrow (Table 7; Appendix 5)

Except for the low dose male group, higher than controls myeloid/erythroid ratios were evidenced in all treated groups of both sexes at the bone marrow smear evaluation performed at the end of the study. The toxicological significance of this finding remains to be ascertained.

5.10 Clinical chemistry (Table 8; Appendix 6)

Most of the differences observed at the clinical chemistry examinations of samples from treated and untreated animals performed at week 6 of the study were already present at the examinations performed before the start of treatment and are to be considered as due to natural intergroup variation.
No consistent intergroup differences were observed at week 13 of the study.

5.11 Urinalysis (Table 9; Appendix 7)

The apparent, non significant, lower than controls specific gravity measured in the treated males, as well as the very high urine glucose concentration observed in the urine of a single animal (male 2350026) at week 13 of the study were not accompanied by variations of related parameters (e.g. blood glucose levels) nor were observed in animals of the other sex. Therefore, they should not be attributed to administration of FDP.

5.12 Faecal occult blood (Appendix 8)

No intergroup variations were observed at the examinations performed during the study.

5.13 Organ weight (Table 10; Appendix 9)

Organ weight analyses revealed statistically significant lower relative kidney weights in females receiving 220 and 440 mg/kg/day and marginally higher than controls relative heart weights in animals of both sexes in all treated groups. Mean relative spleen weights of treated females were also slightly increased. The toxicological significance of these findings remains, however, doubtful as variations were either very small or were present in only one sex.
The remaining differences observed are those commonly seen in laboratory animals and do not have any toxicological significance.

5.14 Macroscopic pathology (Table 11; Appendix 10)

With the exception of the presence of abnormal colour and/areas seen in the intestine of two animals (female 2350021 and male 2340024) receiving 220 mg/kg/day and of one female (2350027) receiving 440 mg/kg/day, there were no changes which were suggestive of a treatment related effect. Doubtful toxicological significance should be attributed to the increased incidence of dark contents in the gall bladder of low and high dose males as this finding was not seen in animals of the other sex.
A slightly increased incidence of dark areas at the injection sites was observed for the treated females, when compared with the controls. No real differences were seen amongst the males. As no evidence of specific treatment related findings was found at the microscopic examination (see below), these changes should be regarded as secondary to the mechanical injury caused by repeated intravenous injections.

5.15 Microscopic pathology (Table 12; Appendix 10)

Mucosal congestion of various portions of the intestine of unclear toxicological significance was observed in one male receiving 110 mg/kg/day, in one male and one female receiving 220 mg/kg/day and in one male and one female receiving 440 mg/kg/day. Evidence of mucosal congestion was also detected in the gall bladder of a single male (2350028) receiving 440 mg/kg/day. In addition, kidney tubular dilatation was observed in one male receiving 440 mg/kg/day.
The presence of haemorrhagic areas at the injection sites of control and treated animals are not to be considered evidence of a toxicological effect, but a consequence of repeated administration by the intravenous route.
The small benign haemangioma detected in the spleen of a male in the intermediate dose group is to be considered as incidental.
The remaining changes were seen as evidence of spontaneous pathology.

6. CONCLUSION

The results of this study indicate that administration of FDP by the intravenous route to dogs for 13 consecutive weeks was generally well tolerated by animals in low- and mid-dose groups. No findings of toxicological significance were observed in animals receiving 110 mg/kg/day. A slightly increased incidence in mild clinical signs and significantly lower than control female relative kidney weights were the only possible indications of a toxic effect seen in animals receiving 220 mg/kg/day.

Indications of a moderate toxic effect were observed in animals receiving 440 mg/kg/day which, in addition to showing a higher incidence of the above mentioned changes, suffered isolated episodes of emesis, salivation and mandibular ptosis. Additional changes of possible toxicological significance limited to animals in the high dose group were a slightly lower than control mean body weight throughout treatment and single cases of gall bladder mucosal congestion and kidney tubular dilatation.

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FDP : 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

FIGURE 1 - Group and pen arrangement in animal rooms

STUDY NO.: 235-003-009

Group: Colour Code	Treatment (mg/kg/day)+	Dogs numbers M (even)	Dogs numbers F (odd)
1: White	0 (Control)	2-8	1-7
2: Yellow	110	10-16	9-15
3: Blue	220	18-24	17-23
4: Red	440	26-32	25-31

Room 6

Group/ sex.	Animal no.	Pen no.	Group/ sex.	Animal no.	Pen no.
1F	9		4M	8	
		01			28
2F	10		3M	7	
		09			20
3F	11		2M	6	
		17			12
4F	12		1M	5	
		25			04
1F	13		4M	4	
		03			26
2F	14		3M	3	
		11			18
3F	15		2M	2	
		19			10
4F	16		1M	1	
		27			02

Room 7

Group/ sex.	Animal no.	Pen no.	Group/ sex.	Animal no.	Pen no.
1F	9		4M	8	
		05			32
2F	10		3M	7	
		13			24
3F	11		2M	6	
		21			16
4F	12		1M	5	
		29			08
1F	13		4M	4	
		07			30
2F	14		3M	3	
		15			22
3F	15		2M	2	
		23			14
4F	16		1M	1	
		31			06

+ = In terms of Fructose-1,6-diphosphate dehydrated sodium salt (FDP Na3H).

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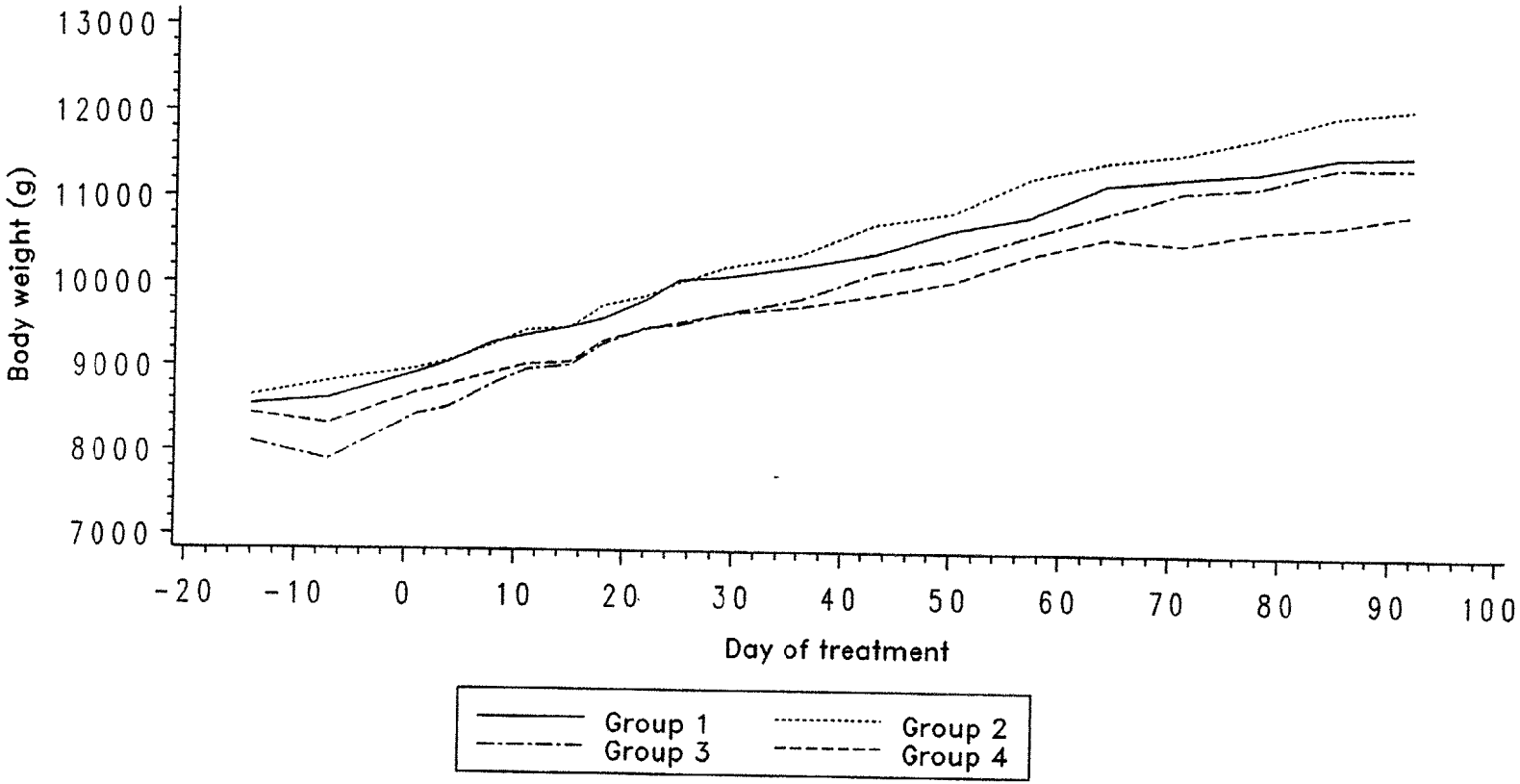
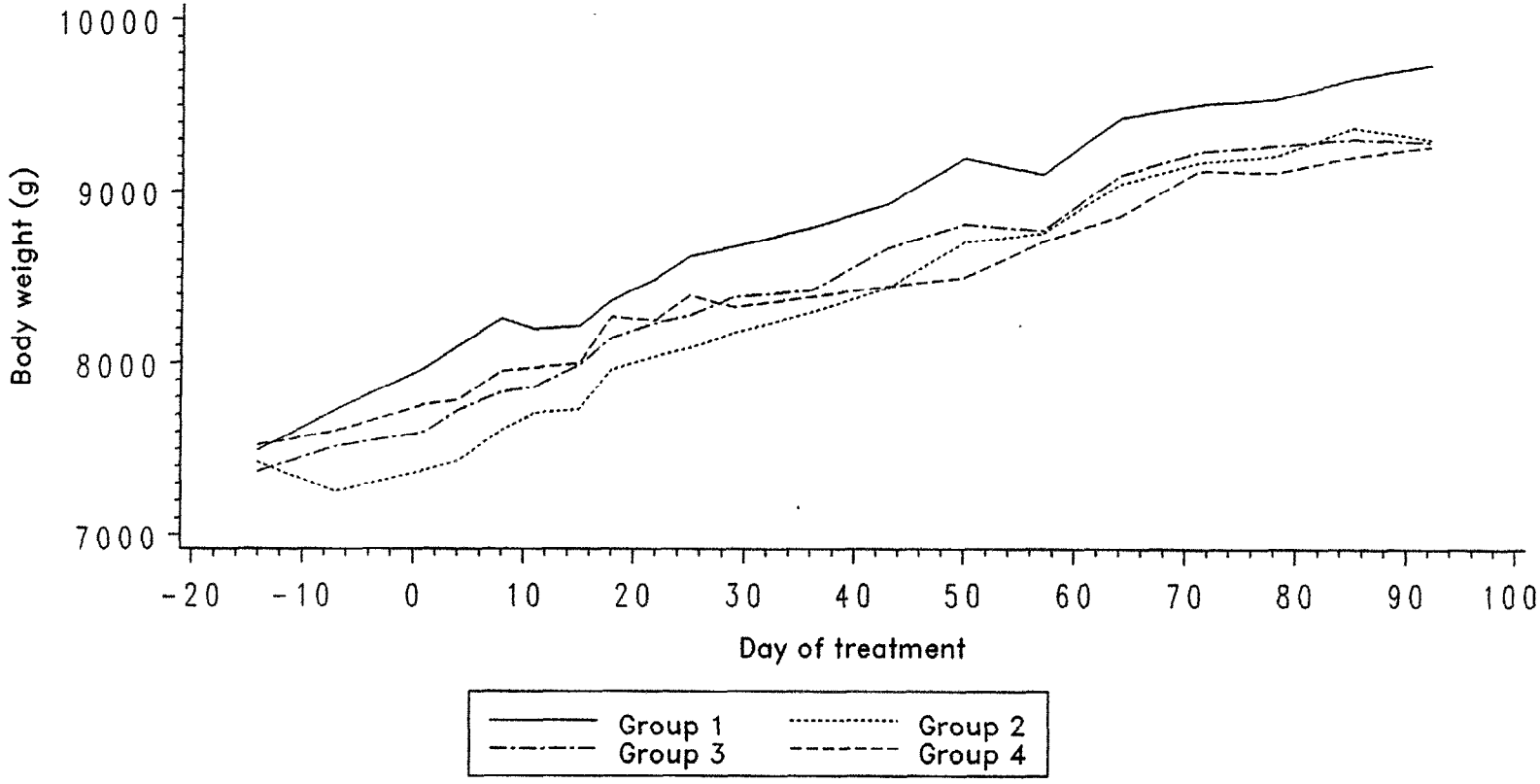
FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS
FIGURE 2A – Body weight versus day of treatment – Males
STUDY NO.: 235–003–009



021

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS
FIGURE 2B – Body weight versus day of treatment – Females
STUDY NO.: 235–003–009



022

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

MALES

Group 1**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	5	3	2	7	1	-	4	2	6	7	6	3	-	2
Tremor/agitation	-	1	-	-	-	3	2	-	-	-	-	-	1	-
Eyes/conjunctivae reddened	-	-	-	-	-	3	2	-	-	-	-	-	1	-
Gums reddened	-	-	-	-	-	3	1	-	-	-	-	-	-	-
Ears reddened	-	-	-	-	-	2	-	-	-	-	-	-	-	7
Salivation	-	-	-	-	-	-	-	1	1	-	-	-	-	-

* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

MALES

Group 2**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	11	17	8	11	10	14	10	9	14	16	14	16	7	12
Tremor/agitation	-	3	-	-	-	-	-	-	-	-	-	-	-	-
Vocalization	-	1	-	-	-	-	1	-	2	-	-	-	-	-
Increased heart rate	-	1	-	1	1	6	1	-	-	-	-	-	-	-
Eyes/conjunctivae reddened	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Gums reddened	-	-	-	2	-	-	1	2	3	1	8	2	3	-
Ears reddened	-	-	-	-	-	-	3	1	-	-	-	2	2	7
Licking lips	-	-	-	-	1	-	-	-	3	-	-	-	-	-
Salivation	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Faeces with mucous and/or blood	-	1	1	-	-	-	-	-	1	-	-	-	-	-

* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

MALES

Group 3**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	14	10	11	14	10	6	8	10	17	11	13	13	16	9
Vocalization	-	1	-	-	-	-	-	-	-	-	3	-	-	-
Increased heart rate	-	1	-	2	2	6	5	1	4	1	-	5	-	-
Licking lips	-	2	4	-	-	-	-	-	1	-	3	-	-	-
Tremors/agitation	-	4	2	-	3	3	7	3	4	3	2	4	3	1
Eyes/conjunctivae reddened	-	1	-	6	5	6	6	-	4	1	5	8	7	13
Gums reddened	-	3	1	6	2	9	4	3	7	2	-	7	9	10
Ears reddened	-	-	1	3	3	9	2	10	14	8	6	9	7	14
Faeces with mucous and/or blood	1	-	-	2	-	-	-	-	-	1	-	-	-	1

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* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

MALES

Group 4**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	6	4	9	5	2	3	6	6	3	9	9	2	6	4
Tremor/agitation	-	6	3	5	3	1	1	2	2	1	-	8	4	-
Increased heart rate	-	1	2	4	12	4	6	4	10	6	6	3	1	-
Salivation	-	1	-	1	-	1	1	-	-	-	-	-	-	1
Licking lips	-	-	3	5	4	2	1	2	6	2	8	-	2	-
Eyes/conjunctivae reddened	-	-	-	6	4	6	9	4	4	4	1	7	8	7
Gums reddened	-	-	-	10	11	7	15	8	4	6	2	13	4	9
Ears reddened	-	-	-	-	-	-	-	2	-	-	-	-	-	14
Emesis	-	-	-	-	-	-	1	-	-	-	-	1	-	-
Faeces with mucous and/or blood	-	-	-	-	-	-	-	1	-	-	-	-	-	-
Vocalization	-	-	1	1	-	-	-	-	4	1	1	1	-	-

* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

FEMALES

Group 1**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	2	-	4	4	1	3	3	4	5	4	10	3	5	3
Faeces with mucous and/or blood	-	-	-	-	-	-	-	1	-	-	-	-	-	-
Tremor/agitation	-	2	1	1	1	3	-	-	1	-	-	-	1	-
Eyes/conjunctivae reddened	-	-	-	-	-	-	-	9	7	9	7	7	7	7
Gums reddened	-	-	-	-	-	-	2	-	-	-	-	-	-	2
Ears reddened	-	-	-	-	-	5	9	7	8	7	7	9	7	-

* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

FEMALES

Group 2**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	6	6	6	6	4	11	5	8	5	7	9	11	7	7
Faeces with mucous and/or blood	2	-	-	-	-	-	-	-	-	-	-	-	-	-
Emesis	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Tremor/agitation	-	2	1	-	-	3	-	3	-	3	-	-	-	-
Eyes/conjunctivae reddened	-	-	-	-	-	4	1	4	2	2	1	-	7	-
Gums reddened	-	1	1	1	7	9	4	6	3	2	4	7	2	8
Ears reddened	-	-	-	-	1	4	-	3	3	-	-	2	-	2
Licking lips	-	-	-	-	2	-	-	4	4	-	-	-	-	2
Increased heart rate	-	-	-	-	1	6	-	1	-	1	1	-	-	-
Salivation	-	-	-	-	-	1	1	-	-	-	-	-	-	-
Head shaking	-	-	-	-	-	-	-	1	1	4	1	2	-	-

* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

FEMALES

Group 3**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	3	6	3	-	-	1	-	4	-	3	5	1	5	-
Tremor/agitation	-	7	4	4	2	2	-	4	1	2	-	2	-	2
Eyes/conjunctivae reddened	-	-	-	-	-	-	-	-	2	1	2	2	1	5
Gums reddened	-	-	7	4	4	4	5	-	1	-	-	5	1	2
Ears reddened	-	-	-	-	-	-	3	-	-	1	9	7	7	14
Licking lips	-	-	-	1	-	-	-	-	-	-	-	-	-	-
Increased heart rate	-	-	-	2	9	4	2	2	2	-	4	-	-	-
Vocalization	-	-	-	-	-	-	-	-	1	-	-	-	-	-
White foam found in kennel	-	-	-	-	-	-	-	-	-	-	-	-	1	-

* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 1 - Clinical signs* - Group incidence

STUDY NO.: 235-003-009

FEMALES

Group 4**

Observation	Pre-dose	Week of study												
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13
Soft faeces/diarrhea	6	1	2	6	5	-	1	2	3	2	-	-	-	2
Tremor/agitation	-	7	9	7	3	5	6	9	8	6	7	8	2	-
Eyes/conjunctivae reddened	-	-	-	7	3	7	7	13	3	2	12	14	20	8
Gums reddened	-	6	6	15	13	15	12	15	11	9	9	13	4	10
Ears reddened	-	-	-	2	-	-	2	5	-	-	-	2	-	6
Licking lips	-	3	6	2	2	-	4	5	3	1	3	-	-	-
Increased heart rate	-	2	-	6	8	4	10	2	10	-	1	1	-	-
Vocalization	-	-	-	-	-	-	-	-	1	1	3	-	-	-
Salivation	-	-	-	-	-	-	2	-	-	-	-	-	1	-

* Signs present at least once daily. Only relevant clinical signs have been reported.
** Number of animals in group = 4

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 2 - Body weights (kg) - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study -14	-7	1	4	8	11	15
1	N	4	4	4	4	4	4	4
	Mean	8.540	8.613	8.920	9.060	9.295	9.378	9.483
	SD	0.368	0.520	0.623	0.653	0.655	0.557	0.624
2	N	4	4	4	4	4	4	4
	Mean	8.645	8.815	8.973	9.065	9.265	9.443	9.478
	SD	0.256	0.145	0.411	0.463	0.459	0.495	0.559
3	N	4	4	4	4	4	4	4
	Mean	8.105	7.890	8.433	8.523	8.795	8.970	9.028
	SD	0.658	0.764	0.846	0.803	0.821	0.787	0.817
4	N	4	4	4	4	4	4	4
	Mean	8.435	8.320	8.685	8.785	8.930	9.033	9.063
	SD	0.640	0.781	0.772	0.756	0.770	0.688	0.846

* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 2 - Body weights (kg) - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study 18	22	25	29	36	43	50
1	N	4	4	4	4	4	4	4
	Mean	9.585	9.810	10.047	10.085	10.213	10.370	10.645
	SD	0.659	0.645	0.512	0.503	0.595	0.488	0.552
2	N	4	4	4	4	4	4	4
	Mean	9.735	9.860	10.020	10.200	10.353	10.715	10.855
	SD	0.540	0.570	0.565	0.652	0.782	0.663	0.687
3	N	4	4	4	4	4	4	4
	Mean	9.270	9.478	9.515	9.650	9.835	10.150	10.325
	SD	0.841	0.858	0.840	0.766	0.942	1.005	1.055
4	N	4	4	4	4	4	4	4
	Mean	9.307	9.465	9.540	9.655	9.745	9.888	10.050
	SD	0.843	0.672	0.683	0.762	0.821	0.743	0.779

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 2 - Body weights (kg) - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study 57	64	71	78	85	92
1	N	4	4	4	4	4	4
	Mean	10.818	11.200	11.280	11.358	11.530	11.560
	SD	0.586	0.620	0.748	0.615	0.584	0.486
2	N	4	4	4	4	4	4
	Mean	11.260	11.463	11.565	11.762	12.020	12.118
	SD	0.787	0.751	0.851	0.799	0.698	0.877
3	N	4	4	4	4	4	4
	Mean	10.602	10.858	11.115	11.185	11.420	11.420
	SD	0.876	1.114	1.050	1.225	1.220	1.378
4	N	4	4	4	4	4	4
	Mean	10.365	10.575	10.510	10.665	10.735	10.880
	SD	0.935	0.979	0.805	0.876	0.817	0.869

* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 2 - Body weights (kg) - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study -14	-7	1	4	8	11	15
1	N	4	4	4	4	4	4	4
	Mean	7.490	7.723	7.965	8.090	8.253	8.190	8.210
	SD	0.423	0.330	0.351	0.424	0.246	0.326	0.411
2	N	4	4	4	4	4	4	4
	Mean	7.420	7.250	7.373	7.425	7.605	7.705	7.725
	SD	0.764	0.711	0.809	0.758	0.750	0.758	0.748
3	N	4	4	4	4	4	4	4
	Mean	7.365	7.510	7.598	7.720	7.825	7.855	7.983
	SD	0.541	0.602	0.510	0.577	0.758	0.716	0.842
4	N	4	4	4	4	4	4	4
	Mean	7.520	7.602	7.753	7.780	7.945	7.968	7.990
	SD	0.417	0.451	0.266	0.238	0.198	0.352	0.343

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 2 - Body weights (kg) - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study 18	22	25	29	36	43	50
1	N	4	4	4	4	4	4	4
	Mean	8.360	8.485	8.620	8.675	8.785	8.923	9.190
	SD	0.462	0.486	0.482	0.540	0.523	0.691	0.677
2	N	4	4	4	4	4	4	4
	Mean	7.955	8.033	8.080	8.170	8.293	8.435	8.703
	SD	0.739	0.647	0.678	0.713	0.774	0.810	0.745
3	N	4	4	4	4	4	4	4
	Mean	8.140	8.227	8.273	8.380	8.415	8.670	8.805
	SD	0.887	0.825	0.867	0.941	1.054	1.057	1.137
4	N	4	4	4	4	4	4	4
	Mean	8.263	8.246	8.390	8.320	8.380	8.445	8.495
	SD	0.155	0.515	0.357	0.455	0.259	0.290	0.310

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 2 - Body weights (kg) - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study 57	64	71	78	85	92
1	N	4	4	4	4	4	4
	Mean	9.097	9.425	9.505	9.535	9.660	9.740
	SD	0.806	0.752	0.982	0.994	1.225	1.298
2	N	4	4	4	4	4	4
	Mean	8.755	9.040	9.165	9.205	9.370	9.300
	SD	0.859	0.865	0.915	1.098	1.113	1.027
3	N	4	4	4	4	4	4
	Mean	8.770	9.093	9.225	9.265	9.305	9.285
	SD	1.068	1.111	0.988	1.003	1.073	1.151
4	N	4	4	4	4	4	4
	Mean	8.705	8.855	9.118	9.108	9.200	9.260
	SD	0.387	0.345	0.179	0.292	0.369	0.241

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 3 - Food consumption+ (g/dog/day) - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study -7	1	8	15	22	29	36	43
1	N	4	4	4	4	4	4	4	4
	Mean	322.89	376.93	385.43	376.07	372.54	381.61	387.07	354.75
	SD	32.78	17.61	26.72	47.86	35.18	21.28	17.31	52.68
2	N	4	4	4	4	4	4	4	4
	Mean	348.96	389.79	400.00	400.00	400.00	393.43	400.00	400.00
	SD	31.49	9.52	0.00	0.00	0.00	13.14	0.00	0.00
3	N	4	4	4	4	4	4	4	4
	Mean	321.86	386.18	400.00	397.86	397.39	400.00	400.00	396.36
	SD	34.79	13.04	0.00	4.28	5.21	0.00	0.00	7.29
4	N	4	4	4	4	4	4	4	4
	Mean	313.68	381.39	382.61	373.39	385.25	374.14	393.29	368.61
	SD	54.97	19.22	34.79	53.21	29.50	51.71	13.43	32.33

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance
+ = mean daily food consumption for the previous 7 days

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 3 - Food consumption+ (g/dog/day) - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study 50	57	64	71	78	85	92
1	N	4	4	4	4	4	4	4
	Mean	394.57	378.75	386.18	365.18	378.61	371.82	362.25
	SD	10.86	42.50	17.45	46.17	25.51	36.64	43.60
2	N	4	4	4	4	4	4	4
	Mean	400.00	400.00	400.00	400.00	400.00	400.00	391.00
	SD	0.00	0.00	0.00	0.00	0.00	0.00	14.94
3	N	4	4	4	4	4	4	4
	Mean	400.00	400.00	399.29	399.29	396.79	381.14	377.71
	SD	0.00	0.00	1.44	1.44	6.43	37.71	34.81
4	N	4	4	4	4	4	4	4
	Mean	387.86	390.82	385.14	381.96	379.18	379.68	339.75
	SD	20.65	18.36	29.71	36.07	41.64	37.38	42.40

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* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance
+ = mean daily food consumption for the previous 7 days

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 3 - Food consumption+ (g/dog/day) - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study -7	1	8	15	22	29	36	43
1	N	4	4	4	4	4	4	4	4
	Mean	328.14	324.82	364.89	368.43	352.25	339.21	365.14	327.25
	SD	17.26	13.64	25.77	42.97	41.20	38.30	34.23	50.10
2	N	4	4	4	4	4	4	4	4
	Mean	315.57	337.29	371.61	376.89	371.25	384.46	383.93	360.61
	SD	32.43	36.42	32.81	35.79	39.39	18.01	24.07	34.17
3	N	4	4	4	4	4	4	4	4
	Mean	331.86	316.39	357.39	349.79	354.54	350.50	365.57	333.00
	SD	40.98	33.87	49.67	32.74	52.65	52.68	35.34	77.44
4	N	4	4	4	4	4	4	4	4
	Mean	307.64	317.43	343.89	328.25	331.29	353.57	378.79	322.89
	SD	37.33	27.28	16.25	60.44	73.40	46.24	26.58	38.01

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance
+ = mean daily food consumption for the previous 7 days

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Roma Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 3 - Food consumption+ (g/dog/day) - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study 50	57	64	71	78	85	92
1	N	4	4	4	4	4	4	4
	Mean	362.86	323.86	354.79	345.21	339.68	318.89	311.21
	SD	38.27	61.54	52.59	33.93	43.74	53.91	48.23
2	N	4	4	4	4	4	4	4
	Mean	386.21	376.93	375.54	370.86	366.36	343.61	333.54
	SD	19.00	30.83	38.16	34.83	39.14	65.34	47.55
3	N	4	4	4	4	4	4	4
	Mean	375.54	362.14	356.39	367.61	372.18	335.11	326.64
	SD	34.66	45.62	50.83	38.97	37.76	47.75	41.67
4	N	4	4	4	4	4	4	4
	Mean	345.57	350.29	364.29	376.54	357.21	317.89	318.00
	SD	49.94	39.57	31.53	23.45	24.83	53.55	9.46

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance
+ = mean daily food consumption for the previous 7 days

Toxicology Centre S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4A - Water consumption (g/dog/day) - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study -14	-13	-12
1	N	4	4	4
	Mean	759.00	946.00	1459.50
	SD	431.07	441.23	252.16
2	N	4	4	4
	Mean	249.25	611.50	558.50*
	SD	115.45	521.73	448.51
3	N	4	4	4
	Mean	644.75	363.50	907.50
	SD	825.40	402.94	415.32
4	N	4	4	4
	Mean	581.25	756.25	1481.25
	SD	340.95	285.31	445.56

* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4A - Water consumption (g/dog/day) - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study -14	-13	-12
1	N	4	4	4
	Mean	470.75	839.75	1062.00
	SD	235.98	87.57	185.75
2	N	4	4	4
	Mean	548.50	671.75	898.75
	SD	99.35	135.05	326.55
3	N	4	4	4
	Mean	991.50	719.75	1148.50
	SD	644.14	174.11	211.99
4	N	4	4	4
	Mean	725.00	713.75	1067.25
	SD	384.34	275.62	362.15

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4B - Water consumption (g/dog/day) - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study -6	-5	-4
1	N	4	4	4
	Mean	607.50	951.00	933.50
	SD	313.48	557.56	120.56
2	N	4	4	4
	Mean	505.75	879.25	636.75
	SD	308.15	496.31	597.25
3	N	4	4	4
	Mean	682.75	1163.50	854.75
	SD	583.01	386.83	788.55
4	N	4	4	4
	Mean	760.75	958.00	1262.00
	SD	345.86	194.87	632.48

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4B - Water consumption (g/dog/day) - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study -6	-5	-4
1	N	4	4	4
	Mean	679.25	1217.75	1050.25
	SD	466.16	623.63	474.32
2	N	4	4	4
	Mean	749.75	714.25	941.00
	SD	461.49	128.21	261.09
3	N	4	4	4
	Mean	702.50	799.00	830.75
	SD	236.58	138.28	146.21
4	N	4	4	4
	Mean	994.75	816.25	999.00
	SD	515.70	21.95	357.03

* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4C - Water consumption (g/dog/day) - Week 1 - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study 2	3	4
1	N	4	4	4
	Mean	918.50	928.00	598.00
	SD	256.52	145.39	335.26
2	N	4	4	4
	Mean	287.00	800.00	1002.25
	SD	300.25	180.95	211.34
3	N	4	4	4
	Mean	1253.25	1404.00	1528.75*
	SD	1030.96	528.90	616.43
4	N	4	4	4
	Mean	1242.50	898.50	1036.50
	SD	669.88	231.77	190.80

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4C - Water consumption (g/dog/day) - Week 1 - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study 2	3	4
1	N	4	4	4
	Mean	1019.25	902.50	1175.25
	SD	805.25	727.95	393.94
2	N	4	4	4
	Mean	725.25	699.00	813.00
	SD	214.38	175.37	77.81
3	N	4	4	4
	Mean	840.25	798.00	779.00
	SD	9.60	158.48	201.18
4	N	4	4	4
	Mean	806.00	631.50	905.00
	SD	94.16	131.70	515.14

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

0.45

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4D - Water consumption (g/dog/day) - Week 7 - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study 43	44	45
1	N	4	4	4
	Mean	836.25	969.50	1128.00
	SD	147.56	329.15	653.77
2	N	4	4	4
	Mean	588.75	1243.25	1330.75
	SD	224.23	323.30	437.32
3	N	4	4	4
	Mean	1078.25	1445.25	1221.50
	SD	444.20	510.82	403.90
4	N	4	4	4
	Mean	861.75	922.50	1282.75
	SD	394.40	251.28	410.22

* = mean value of group was significantly different from control at $p < 0.05$ with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4D - Water consumption (g/dog/day) - Week 7 - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study 43	44	45
1	N	4	4	4
	Mean	800.25	728.50	753.25
	SD	419.84	259.90	281.06
2	N	4	4	4
	Mean	758.00	933.75	795.00
	SD	413.32	297.56	184.78
3	N	4	4	4
	Mean	739.50	810.50	782.00
	SD	257.80	105.19	124.86
4	N	4	4	4
	Mean	594.25	975.75	666.50
	SD	142.79	437.91	190.69

* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4E - Water consumption (g/dog/day) - Week 12 - Mean data

STUDY NO.: 235-003-009

MALES

Group		Day of Study 78	79	80
1	N	4	4	4
	Mean	1398.00	1159.00	1350.25
	SD	646.02	615.36	696.51
2	N	4	4	4
	Mean	1039.50	1318.75	734.50
	SD	224.86	120.03	184.32
3	N	4	4	4
	Mean	1086.00	1198.75	1064.50
	SD	235.80	355.44	395.50
4	N	4	4	4
	Mean	1031.50	886.25	1005.00
	SD	155.22	152.13	123.10

* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 4E - Water consumption (g/dog/day) - Week 12 - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Day of Study 78	79	80
1	N	4	4	4
	Mean	751.00	695.75	631.75
	SD	365.59	248.00	341.71
2	N	4	4	4
	Mean	883.25	889.00	791.75
	SD	239.75	247.97	279.05
3	N	4	4	4
	Mean	887.50	480.25	1154.75
	SD	500.83	234.15	619.97
4	N	4	4	4
	Mean	645.00	886.75	740.75
	SD	192.01	468.96	223.08

* = mean value of group was significantly different from control at p < 0.05 with Dunnett's test of significance

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 5 - Observation during administration - Group incidence +

STUDY NO.: 235-003-009

Group	Males	Females
1	0/4	0/4
2	2/4	1/4
3	2/4	3/4
4	3/4	4/4

+ Number of animals, out of 4, that showed tachycardia during the administration of the test substance on day 56 and 58 of the treatment period.

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 6 - Ophthalmoscopy - Group incidence +

STUDY NO.: 235-003-009

Week	Observation	Group/Sex 1M	2M	3M	4M	1F	2F	3F	4F
-2	NAD	4	4	4	4	4	4	4	4
6	NAD	4	4	4	4	4	4	3	4
	Keratitis	0	0	0	0	0	0	1	0
12	NAD	4	4	4	4	4	4	4	4

NAD No abnormality detected
+ Numbers represent the number of animals, out of 4, that showed the above signs

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7A - Haematology - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	-13	2.00	2.45	4	0.75	1.50	4	6.25	4.79	4	0.00	0.00	4
RED BLOOD CELL COUNT 10'6/cmm	-13	6.04	0.49	4	5.64	0.35	4	6.11	0.28	4	5.67	0.16	4
HAEMOGLOBIN g/dl	-13	12.825	1.063	4	12.050	0.957	4	13.225	0.660	4	12.125	0.263	4
HAEMATOCRIT %	-13	43.05	3.10	4	39.78	2.56	4	42.58	2.23	4	39.73	1.40	4
MEAN RBC CELL VOLUME fl	-13	71.50	0.58	4	70.50	2.38	4	69.75	0.96	4	70.25	2.06	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	-13	21.23	0.62	4	21.40	1.54	4	21.65	0.54	4	21.40	0.29	4
MEAN CORPUSCULAR Hb CONC. g/dl	-13	29.80	0.77	4	30.30	1.12	4	31.05	0.65	4	30.53	0.66	4
PLATELETS 10'3/cmm	-13	437.25	107.03	4	504.50	79.73	4	506.50	103.36	4	453.25	37.42	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7A - Haematology - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
WHITE BLOOD CELL COUNT 10'3/cmm	-13 (n)	13.70	6.58	4	12.98	1.32	4	13.18	3.04	4	11.85	1.09	4
NEUTROPHILS %	-13	63.25	12.34	4	65.25	3.86	4	72.25	12.45	4	72.00	6.48	4
LYMPHOCYTES %	-13	32.75	11.09	4	32.50	3.32	4	23.50	7.37	4	25.75	6.13	4
EOSINOPHILS %	-13	4.00	2.16	4	2.00	1.83	4	3.75	6.24	4	1.75	1.71	4
MONOCYTES %	-13	0.00	0.00	4	0.25	0.50	4	0.50	0.58	4	0.50	0.58	4
BASOPHILS %	-13	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7A - Haematology - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control			Group 2			Group 3			Group 4		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
PROTHROMBIN TIME sec	-13	9.55	0.06	4	9.58	0.17	4	9.60	0.14	4	9.58	0.10	4
PARTIAL THROMBOPLASTIN TIME sec	-13	12.10	0.63	4	13.33	1.26	4	12.68	0.90	4	12.85	0.90	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7A - Haematology - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	-13	0.00	0.00	4	0.00	0.00	4	2.00	2.45	4	0.75	1.50	4
RED BLOOD CELL COUNT 10'6/cmm	-13	5.75	0.36	4	5.83	0.33	4	5.68	0.69	4	6.29	0.52	4
HAEMOGLOBIN g/dl	-13	12.600	0.829	4	13.025	0.544	4	12.100	1.203	4	13.775	1.103	4
HAEMATOCRIT %	-13	40.85	1.98	4	41.75	1.84	4	40.23	5.15	4	44.60	3.57	4
MEAN RBC CELL VOLUME fl	-13	71.00	0.82	4	71.50	1.73	4	70.50	1.00	4	70.75	0.96	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	-13	21.93	0.61	4	22.40	1.35	4	21.33	1.10	4	21.90	0.78	4
MEAN CORPUSCULAR Hb CONC. g/dl	-13	30.85	0.90	4	31.20	1.08	4	30.20	1.41	4	30.90	0.73	4
PLATELETS 10'3/cmm	-13	476.75	54.73	4	460.25	77.53	4	400.75	27.60	4	439.75	41.39	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7A - Haematology - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
WHITE BLOOD CELL COUNT 10'3/cmm	-13	10.57	2.39	4	12.63	3.26	4	10.75	0.91	4	13.13	3.08	4
NEUTROPHILS %	-13	69.50	1.73	4	74.75	2.75	4	75.75	4.57	4	74.25	5.06	4
LYMPHOCYTES %	-13	28.00	2.71	4	23.50	3.87	4	22.75	4.50	4	25.25	4.57	4
EOSINOPHILS %	-13	2.25	1.50	4	1.50	1.91	4	1.50	1.29	4	0.50	1.00	4
MONOCYTES %	-13	0.25	0.50	4	0.25	0.50	4	0.00	0.00	4	0.00	0.00	4
BASOPHILS %	-13	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7A - Haematology - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
PROTHROMBIN TIME sec	-13	9.83	0.25	4	9.98	0.21	4	9.75	0.10	4	9.80	0.14	4
PARTIAL THROMBOPLASTIN TIME sec	-13	12.35	0.82	4	13.50	0.42	4	13.25	1.06	4	13.00	0.42	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

?DP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7B - Haematology - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	-5	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4
RED BLOOD CELL COUNT 10'6/cmm	-5	6.15	0.38	4	5.78	0.22	4	6.15	0.45	4	6.04	0.51	4
HAEMOGLOBIN g/dl	-5	13.525	0.538	4	12.475	0.943	4	13.450	0.480	4	13.075	0.519	4
HAEMATOCRIT %	-5	43.67	2.35	4	40.70	2.28	4	42.88	3.24	4	42.50	3.28	4
MEAN RBC CELL VOLUME fl	-5	71.25	0.96	4	70.50	1.73	4	69.75	0.50	4	70.50	1.73	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	-5	22.05	0.60	4	21.58	1.14	4	21.90	0.86	4	21.73	1.06	4
MEAN CORPUSCULAR Hb CONC. g/dl	-5	31.00	0.65	4	30.65	0.84	4	31.43	1.30	4	30.83	1.30	4
PLATELETS 10'3/cmm	-5	435.25	67.34	4	531.50	50.89	4	480.00	84.08	4	471.00	32.84	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7B - Haematology - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
WHITE BLOOD CELL COUNT 10'3/cmm	-5	11.10	1.37	4	10.03	1.10	4	10.20	2.31	4	9.08	1.28	4
NEUTROPHILS %	-5	60.25	12.15	4	58.50	11.62	4	66.75	10.14	4	59.25	2.99	4
LYMPHOCYTES %	-5	35.00	8.68	4	37.00	11.20	4	28.75	5.85	4	36.50	2.65	4
EOSINOPHILS %	-5	4.50	4.36	4	4.50	1.73	4	4.00	4.90	4	3.75	4.11	4
MONOCYTES %	-5	0.25	0.50	4	0.00	0.00	4	0.50	0.58	4	0.50	0.58	4
BASOPHILS %	-5	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7B - Haematology - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
PROTHROMBIN TIME sec	-5	9.80	0.40	4	9.75	0.24	4	9.78	0.17	4	9.85	0.17	4
PARTIAL THROMBOPLASTIN TIME sec	-5	11.75	0.24	4	12.68	0.68	4	12.53	0.61	4	12.25	1.11	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7B - Haematology - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	-5	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4
RED BLOOD CELL COUNT 10'6/cmm	-5	6.03	0.28	4	5.85	0.18	4	6.03	0.82	4	6.49	0.50	4
HAEMOGLOBIN g/dl	-5	13.375	0.634	4	12.875	1.144	4	12.925	1.307	4	14.525	1.258	4
HAEMATOCRIT %	-5	42.90	1.90	4	41.68	2.25	4	42.70	6.00	4	45.78	3.77	4
MEAN RBC CELL VOLUME fl	-5	71.00	0.82	4	71.00	2.16	4	71.00	0.82	4	70.50	1.00	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	-5	22.23	0.93	4	21.98	1.28	4	21.53	0.96	4	22.38	0.43	4
MEAN CORPUSCULAR Hb CONC. g/dl	-5	31.18	1.26	4	30.85	1.29	4	30.40	1.42	4	31.70	0.22	4
PLATELETS 10'3/cmm	-5	480.75	53.46	4	450.25	56.96	4	382.00	44.46	4	414.00	65.51	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7B - Haematology - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
WHITE BLOOD CELL COUNT 10'3/cmm	-5	10.88	1.23	4	8.20*	1.47	4	7.55*	0.64	4	10.43	1.84	4
NEUTROPHILS %	-5	65.25	9.22	4	61.75	11.41	4	65.50	11.79	4	64.75	8.54	4
LYMPHOCYTES %	-5	32.50	9.47	4	36.75	11.32	4	32.50	11.09	4	33.25	8.38	4
EOSINOPHILS %	-5	2.25	0.96	4	1.25	0.96	4	1.50	1.73	4	2.00	1.41	4
MONOCYTES %	-5	0.00	0.00	4	0.25	0.50	4	0.50	0.58	4	0.00	0.00	4
BASOPHILS %	-5	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7B - Haematology - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
PROTHROMBIN TIME sec	-5	10.05	0.35	4	9.93	0.13	4	10.00	0.12	4	10.03	0.10	4
PARTIAL THROMBOPLASTIN TIME sec	-5	12.13	0.80	4	12.85	0.54	4	12.45	0.33	4	12.70	0.74	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7C - Haematology - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	42		0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4
RED BLOOD CELL COUNT 10'6/cmm	42	(n)	6.80	0.31	4	6.27*	0.03	4	6.68	0.25	4	6.85	0.19	4
HAEMOGLOBIN g/dl	42		14.975	0.763	4	13.175**	0.585	4	14.800	0.739	4	15.200	0.183	4
HAEMATOCRIT %	42		49.50	2.00	4	44.70**	0.64	4	47.30	2.12	4	49.08	1.16	4
MEAN RBC CELL VOLUME fl	42		73.00	0.82	4	71.25	0.96	4	70.75	1.26	4	71.75	2.06	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	42		22.00	0.47	4	21.05	0.90	4	22.15	0.44	4	22.20	0.41	4
MEAN CORPUSCULAR Hb CONC. g/dl	42		30.25	0.77	4	29.45	0.93	4	31.30	0.37	4	31.00	0.57	4
PLATELETS 10'3/cmm	42		261.25	73.69	4	357.50	29.10	4	303.25	104.31	4	318.00	21.65	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7C - Haematology - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
WHITE BLOOD CELL COUNT 10'3/cmm	42	9.65	2.59	4	10.18	0.64	4	11.13	3.33	4	9.90	1.08	4
NEUTROPHILS %	42	64.00	11.80	4	56.75	12.18	4	63.75	8.42	4	62.00	9.59	4
LYMPHOCYTES %	42	32.25	11.87	4	39.75	12.20	4	32.00	4.69	4	32.25	9.32	4
EOSINOPHILS %	42	2.75	2.22	4	2.75	1.50	4	4.00	6.73	4	5.00	2.94	4
MONOCYTES %	42	1.00	2.00	4	0.75	0.96	4	0.25	0.50	4	0.75	0.50	4
BASOPHILS %	42	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7C - Haematology - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
PROTHROMBIN TIME sec	42	9.73	0.36	4	9.53	0.33	4	9.60	0.22	4	9.65	0.26	4
PARTIAL THROMBOPLASTIN TIME sec	42	12.35	0.17	4	13.50	0.76	4	12.90	0.67	4	12.95	0.66	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7C - Haematology - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	Control SD	N	Group 2 Mean	Group 2 SD	N	Group 3 Mean	Group 3 SD	N	Group 4 Mean	Group 4 SD	N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	42		0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4
RED BLOOD CELL COUNT 10'6/cmm	42		6.88	0.52	4	6.53	0.32	4	7.05	0.79	4	7.54	0.68	4
HAEMOGLOBIN g/dl	42		15.425	1.072	4	14.725	1.050	4	15.275	2.019	4	16.375	1.193	4
HAEMATOCRIT %	42		49.78	4.25	4	47.28	2.63	4	50.65	5.59	4	54.10	4.50	4
MEAN RBC CELL VOLUME fl	42		72.50	1.00	4	72.25	2.63	4	71.75	0.96	4	72.00	1.41	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	42		22.43	0.70	4	22.55	0.99	4	21.65	1.47	4	21.77	1.37	4
MEAN CORPUSCULAR Hb CONC. g/dl	42		31.03	1.00	4	31.13	0.74	4	30.13	1.74	4	30.30	1.40	4
PLATELETS 10'3/cmm	42	(n)	295.00	8.29	4	297.75	34.24	4	267.25	43.71	4	296.50	79.27	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7C - Haematology - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
WHITE BLOOD CELL COUNT 10'3/cmm	42	(n)	9.45	1.84	4	11.23	6.40	4	9.05	0.73	4	9.88	1.32	4
NEUTROPHILS %	42		60.50	3.51	4	70.25	12.34	4	70.50	8.35	4	61.75	11.24	4
LYMPHOCYTES %	42		32.00	4.08	4	28.00	11.49	4	26.50	6.66	4	36.00	11.46	4
EOSINOPHILS %	42		6.00	2.94	4	0.75**	0.96	4	2.25*	2.22	4	1.75*	0.96	4
MONOCYTES %	42		1.50	0.58	4	1.00	1.41	4	0.75	0.50	4	0.50	0.58	4
BASOPHILS %	42		0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7C - Haematology - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
PROTHROMBIN TIME sec	42	9.90	0.51	4	9.32	0.26	4	9.78	0.43	4	9.48	0.15	4
PARTIAL THROMBOPLASTIN TIME sec	42	12.80	0.91	4	13.10	0.36	4	12.95	0.44	4	13.05	0.60	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7D - Haematology - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	86		0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4
RED BLOOD CELL COUNT 10'6/cmm	86		6.98	0.36	4	6.43	0.26	4	7.14	1.00	4	6.91	0.40	4
HAEMOGLOBIN g/dl	86		15.725	1.144	4	14.400	0.594	4	16.000	2.195	4	15.525	0.776	4
HAEMATOCRIT	86	(n)	48.90	1.87	4	44.25*	1.47	4	49.15	7.67	4	47.83	2.67	4
MEAN RBC CELL VOLUME fl	86		70.25	0.96	4	69.00	1.41	4	68.50	1.73	4	69.25	1.50	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	86		22.52	0.63	4	22.38	1.10	4	22.40	0.53	4	22.45	0.90	4
MEAN CORPUSCULAR Hb CONC. g/dl	86		32.13	1.12	4	32.53	0.92	4	32.65	1.13	4	32.48	1.15	4
PLATELETS 10'3/cmm	86		247.50	49.68	4	323.00	20.07	3	275.75	88.53	4	295.00	31.91	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7D - Haematology - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
WHITE BLOOD CELL COUNT 10'3/cmm	86		9.33	1.20	4	11.00	1.67	4	11.95	1.30	4	12.10	1.86	4
NEUTROPHILS %	86		59.50	7.72	4	56.75	9.88	4	63.00	16.69	4	68.50	4.93	4
LYMPHOCYTES %	86		35.50	7.85	4	40.50	9.68	4	30.00	11.49	4	27.25	6.29	4
EOSINOPHILS %	86	(n)	3.75	1.26	4	2.75	1.50	4	6.50	9.75	4	3.75	2.36	4
MONOCYTES %	86		1.25	1.26	4	0.00	0.00	4	0.50	0.58	4	0.50	0.58	4
BASOPHILS %	86		0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7D - Haematology - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
PROTHROMBIN TIME sec	86	9.68	0.32	4	9.68	0.55	4	9.40	0.48	4	9.75	0.52	4
PARTIAL THROMBOPLASTIN TIME sec	86	12.08	0.53	4	12.93	1.05	4	12.70	0.82	4	12.83	0.91	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7D - Haematology - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ERYTHROCYTE SEDIMENTATION RATE mm/hour	86	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4
RED BLOOD CELL COUNT 10'6/cmm	86	6.69	0.49	4	6.82	0.21	4	7.11	0.25	4	7.03	0.28	4
HAEMOGLOBIN g/dl	86	15.400	1.337	4	15.875	0.263	4	16.175	0.695	4	16.250	1.173	4
HAEMATOCRIT %	86	46.88	4.04	4	47.55	1.01	4	49.58	2.17	4	49.13	2.57	4
MEAN RBC CELL VOLUME fl	86	70.00	0.82	4	69.75	2.50	4	69.50	1.00	4	70.00	1.41	4
MEAN CORPUSCULAR HAEMOGLOBIN pg	86	23.03	0.35	4	23.28	0.88	4	22.75	0.76	4	23.10	0.76	4
MEAN CORPUSCULAR Hb CONC. g/dl	86	32.85	0.48	4	33.40	0.66	4	32.63	0.94	4	33.08	0.78	4
PLATELETS 10'3/cmm	86	274.00	26.19	4	288.25	42.43	4	271.75	35.34	4	277.00	51.88	4

Controls from group(s): 1

Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test

(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance

* Indicates group mean is significantly different from control at level P = .05

** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

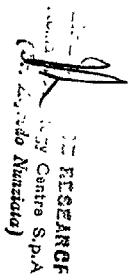
TABLE 7D - Haematology - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
WHITE BLOOD CELL COUNT 10'3/cmm	86		11.23	3.03	4	10.38	2.92	4	9.45	0.61	4	10.52	2.09	4
NEUTROPHILS %	86		62.00	8.49	4	58.50	3.51	4	66.75	5.56	4	58.25	2.63	4
LYMPHOCYTES %	86		32.50	4.12	4	38.25	4.99	4	33.00	5.72	4	38.25	2.87	4
EOSINOPHILS %	86	(n)	5.50	4.43	4	2.50	1.00	4	0.25	0.50	4	3.25	2.63	4
MONOCYTES %	86		0.00	0.00	4	0.75	0.96	4	0.00	0.00	4	0.25	0.50	4
BASOPHILS %	86		0.00	0.00	4	0.00	0.00	4	0.00	0.00	4	0.00	0.00	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01



FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7D - Haematology - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
PROTHROMBIN TIME sec	86	9.43	0.25	4	9.28	0.21	4	9.43	0.35	4	9.55	0.19	4
PARTIAL THROMBOPLASTIN TIME sec	86	12.60	0.65	4	13.03	0.39	4	12.40	0.39	4	12.53	0.22	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7E - Haematology - Bone marrow smear evaluation - Mean data

STUDY NO.: 235-003-009

MALES

Group		Myeloid cells %	Erythroid cells %	Ratio M/E
1	N	4	4	4
	Mean	63.25	36.75	1.73
	SD	2.06	2.06	0.15
2	N	4	4	4
	Mean	63.25	36.75	1.73
	SD	2.21	2.22	0.15
3	N	4	4	4
	Mean	66.25	33.75	1.98
	SD	2.62	2.63	0.24
4	N	4	4	4
	Mean	65.50	34.50	1.90
	SD	1.29	1.29	0.11

* mean value of group was significantly different from control at $p<0.05$ with Dunnett's test of significance

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 7E - Haematology - Bone marrow smear evaluation - Mean data

STUDY NO.: 235-003-009

FEMALES

Group		Myeloid cells %	Erythroid cells %	Ratio M/E
1	N	4	4	4
	Mean	62.00	38.00	1.63
	SD	1.83	1.83	0.12
2	N	4	4	4
	Mean	66.50*	33.50*	2.01*
	SD	3.11	3.11	0.30
3	N	4	4	4
	Mean	64.25	35.75	1.81
	SD	2.22	2.22	0.18
4	N	4	4	4
	Mean	65.50	34.50	1.91
	SD	2.65	2.65	0.22

* mean value of group was significantly different from control at $p<0.05$ with Dunnett's test of significance

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8A - Clinical chemistry - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
ALKALINE PHOSPHATASE U/l	-13	(n)	191.70	29.78	4	211.41	53.55	4	239.97	25.42	4	285.95	144.46	4
ALANINE TRANSFERASE U/l	-13		18.12	3.89	4	17.07	3.58	4	16.08	1.46	4	20.26	6.01	4
ASPARTATE TRANSFERASE U/l	-13		10.42	3.41	4	11.50	4.11	4	10.25	0.63	4	10.69	1.79	4
UREA mg/dl	-13		28.62	9.57	4	28.18	5.61	4	24.71	2.53	4	27.09	7.21	4
GLUCOSE mg/dl	-13		95.97	3.51	4	100.42	10.02	4	103.81	3.76	4	98.32	10.85	4
TOTAL BILIRUBIN mg/dl	-13		0.1000	0.0200	4	0.0950	0.0100	4	0.0950	0.0058	4	0.0950	0.0238	4
TOTAL CHOLESTEROL mg/dl	-13		170.78	30.80	4	161.11	17.75	4	184.11	30.89	4	168.65	13.42	4
CREATININE mg/dl	-13		0.72	0.07	4	0.75	0.08	4	0.75	0.07	4	0.80	0.05	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8A - Clinical chemistry - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
TOTAL PROTEIN g/dl	-13	5.62	0.31	4	5.69	0.30	4	5.90	0.41	4	5.64	0.07	4
ALBUMIN %	-13	59.58	3.56	4	59.40	2.42	4	57.30	3.54	4	60.20	1.30	4
ALPHA 1 GLOBULIN %	-13	5.43	0.53	4	5.10	0.37	4	5.10	0.28	4	5.13	0.42	4
ALPHA 2 GLOBULIN %	-13	6.40	0.73	4	6.08	0.78	4	7.33	0.65	4	7.18	0.36	4
BETA GLOBULIN %	-13	11.35	0.70	4	14.15	2.62	4	11.70	1.73	4	10.48	1.08	4
GAMMA GLOBULIN %	-13	17.27	2.43	4	15.25	1.61	4	18.55	1.77	4	17.02	0.32	4
ALBUMIN/GLOBULIN RATIO	-13	1.488	0.221	4	1.473	0.148	4	1.355	0.205	4	1.518	0.081	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8A - Clinical chemistry - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
CHLORIDE mmol/l	-13	96.02	1.05	4	96.32	1.99	4	96.53	3.46	4	98.61	1.71	4
SODIUM mmol/l	-13	145.000	1.359	4	144.850	1.644	4	143.375	1.189	4	143.550	0.591	4
POTASSIUM mmol/l	-13/ 1(n)	4.740	0.488	4	4.955	0.031	4	5.020	0.368	4	4.793	0.190	4
CALCIUM mmol/l	-13/ 1(n)	2.685	0.073	4	2.775	0.006	4	2.658	0.084	4	2.575	0.054	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8A - Clinical chemistry - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ALKALINE PHOSPHATASE U/l	-13		210.10	47.81	4	185.24	38.69	4	209.53	98.66	4	180.38	22.49	4
ALANINE TRANSFERASE U/l	-13		16.68	5.46	4	17.44	0.78	4	19.82	2.33	4	17.89	3.04	4
ASPARTATE TRANSFERASE U/l	-13		10.14	1.27	4	12.35	2.09	4	10.04	1.88	4	10.84	1.25	4
UREA mg/dl	-13		30.70	1.83	4	28.54	2.79	4	30.32	4.92	4	30.55	4.45	4
GLUCOSE mg/dl	-13		95.04	7.42	4	92.41	7.56	4	98.30	3.97	4	92.49	5.11	4
TOTAL BILIRUBIN mg/dl	-13	(n)	0.0825	0.0275	4	0.0675	0.0395	4	0.0825	0.0050	4	0.0850	0.0173	4
TOTAL CHOLESTEROL mg/dl	-13	(n)	181.56	27.66	4	132.26	15.06	4	150.63	4.40	4	156.89	4.93	4
CREATININE mg/dl	-13		0.78	0.05	4	0.57**	0.05	4	0.59**	0.07	4	0.61**	0.05	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8A - Clinical chemistry - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
TOTAL PROTEIN g/dl	-13	5.68	0.15	4	5.47	0.22	4	5.74	0.18	4	5.89	0.39	4
ALBUMIN %	-13	60.88	1.56	4	61.88	1.37	4	60.53	3.13	4	60.55	3.21	4
ALPHA 1 GLOBULIN %	-13	5.13	0.34	4	5.23	0.46	4	4.90	0.33	4	4.88	0.30	4
ALPHA 2 GLOBULIN %	-13	6.38	1.12	4	5.90	0.62	4	5.98	0.46	4	6.30	0.88	4
BETA GLOBULIN %	-13	10.40	0.73	4	10.15	1.80	4	10.30	0.96	4	9.45	0.81	4
GAMMA GLOBULIN %	-13	17.20	0.77	4	16.90	3.06	4	18.27	1.83	4	18.83	2.44	4
ALBUMIN/GLOBULIN RATIO	-13	1.560	0.101	4	1.623	0.093	4	1.545	0.213	4	1.548	0.206	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8A - Clinical chemistry - Before treatment [1] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
CHLORIDE mmol/l	-13	(n)	95.33	0.22	4	97.98	5.33	4	96.38	3.21	4	96.14	2.76	4
SODIUM mmol/l	-13		142.625	0.545	4	142.425	1.031	4	141.125	1.522	4	142.200	1.394	4
POTASSIUM mmol/l	-13		4.813	0.228	4	4.263	0.373	4	4.463	0.373	4	4.858	0.601	4
CALCIUM mmol/l	-13		2.633	0.116	4	2.668	0.049	4	2.718	0.079	4	2.725	0.050	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8B - Clinical chemistry - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
ALKALINE PHOSPHATASE U/l	-5	(n)	197.84	29.83	4	195.99	42.74	4	240.67	28.86	4	291.96	139.32	4
ALANINE TRANSFERASE U/l	-5		17.11	4.41	4	15.43	3.42	4	15.75	2.27	4	18.79	5.89	4
ASPARTATE TRANSFERASE U/l	-5	(n)	8.72	1.05	4	8.70	1.59	4	11.99	5.01	4	10.43	0.77	4
UREA mg/dl	-5		22.16	3.86	4	22.60	4.06	4	23.61	5.07	4	25.41	1.87	4
GLUCOSE mg/dl	-5		93.56	3.22	4	97.72	6.85	4	96.58	5.33	4	95.01	10.66	4
TOTAL BILIRUBIN mg/dl	-5		0.0875	0.0171	4	0.0900	0.0141	4	0.0900	0.0374	4	0.0900	0.0141	4
TOTAL CHOLESTEROL mg/dl	-5		181.85	21.03	4	162.02	7.78	4	175.09	39.32	4	161.10	13.25	4
CREATININE mg/dl	-5		0.60	0.05	4	0.62	0.04	4	0.66	0.06	4	0.65	0.04	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8B - Clinical chemistry - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
TOTAL PROTEIN g/dl	-5		5.61	0.14	4	5.54	0.31	4	5.67	0.50	4	5.54	0.23	4
ALBUMIN %	-5		62.53	1.95	4	61.35	2.65	4	60.33	3.93	4	63.15	0.93	4
ALPHA 1 GLOBULIN %	-5		4.65	0.26	4	4.48	0.29	4	4.50	0.42	4	4.35	0.21	4
ALPHA 2 GLOBULIN %	-5		7.20	0.50	4	6.78	0.77	4	7.55	1.17	4	7.60	0.28	4
BETA GLOBULIN %	-5	(n)	9.45	0.06	4	12.83	2.26	4	10.30	1.47	4	9.18	0.85	4
GAMMA GLOBULIN %	-5		16.13	1.92	4	14.60	2.33	4	17.30	1.97	4	15.73	0.38	4
ALBUMIN/GLOBULIN RATIO	-5		1.675	0.141	4	1.595	0.185	4	1.540	0.264	4	1.715	0.068	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

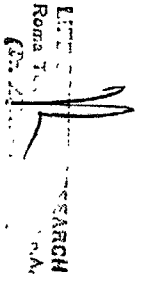
TABLE 8B - Clinical chemistry - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
CHLORIDE mmol/l	-5	98.87	3.78	4	99.58	2.78	4	99.64	2.24	4	98.72	1.88	4
SODIUM mmol/l	-5	145.475	1.262	4	145.275	1.072	4	146.150	1.932	4	146.150	0.946	4
POTASSIUM mmol/l	-5	5.278	0.255	4	5.430	0.181	4	5.398	0.832	4	5.255	0.382	4
CALCIUM mmol/l	-5	2.890	0.089	4	2.903	0.070	4	2.845	0.090	4	2.900	0.043	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01



FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8B - Clinical chemistry - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	Control SD	N	Group 2 Mean	Group 2 SD	N	Group 3 Mean	Group 3 SD	N	Group 4 Mean	Group 4 SD	
ALKALINE PHOSPHATASE U/l	-5		192.02	35.04	4	189.25	32.25	4	203.01	90.25	4	172.40	26.79	4
ALANINE TRANSFERASE U/l	-5		16.62	3.07	4	14.77	2.42	4	16.11	1.79	4	15.81	2.21	4
ASPARTATE TRANSFERASE U/l	-5		8.85	0.78	4	9.47	1.52	4	9.38	1.57	4	10.32	1.99	4
UREA mg/dl	-5	(n)	22.91	13.07	4	21.64	2.36	4	26.39	1.40	4	23.24	1.76	4
GLUCOSE mg/dl	-5		95.56	3.84	4	98.16	4.18	4	96.13	4.28	4	94.86	3.31	4
TOTAL BILIRUBIN mg/dl	-5		0.0950	0.0173	4	0.0975	0.0096	4	0.1050	0.0191	4	0.1225	0.0096	4
TOTAL CHOLESTEROL mg/dl	-5		177.24	22.99	4	144.45*	9.88	4	149.57	13.46	4	147.74*	11.40	4
CREATININE mg/dl	-5		0.60	0.05	4	0.60	0.02	4	0.64	0.09	4	0.66	0.07	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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Roma Toxicology Centro S.p.A.
(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8B - Clinical chemistry - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
TOTAL PROTEIN g/dl	-5	5.56	0.07	4	5.43	0.23	4	5.62	0.23	4	5.71	0.31	4
ALBUMIN %	-5	64.53	1.60	4	64.05	0.62	4	63.30	2.81	4	63.55	2.52	4
ALPHA 1 GLOBULIN %	-5	4.47	0.41	4	4.65	0.17	4	4.30	0.37	4	4.45	0.21	4
ALPHA 2 GLOBULIN %	-5	6.05	0.79	4	5.93	0.46	4	6.05	0.29	4	5.98	0.77	4
BETA GLOBULIN %	-5	9.35	0.94	4	9.30	1.56	4	9.30	1.05	4	8.48	0.49	4
GAMMA GLOBULIN %	-5	15.65	1.14	4	16.05	2.33	4	17.02	1.42	4	17.55	2.18	4
ALBUMIN/GLOBULIN RATIO	-5	1.825	0.130	4	1.785	0.048	4	1.738	0.213	4	1.750	0.188	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8B - Clinical chemistry - Before treatment [2] - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
CHLORIDE mmol/l	-5		96.80	0.62	4	102.00**	2.42	4	100.03	2.02	4	99.93	1.45	4
SODIUM mmol/l	-5		145.325	0.650	4	144.450	0.617	4	143.650*	1.156	4	144.925	0.755	4
POTASSIUM mmol/l	-5	(n)	5.003	0.067	4	4.570	0.436	4	4.530**	0.112	4	4.783	0.393	4
CALCIUM mmol/l	-5		2.900	0.037	4	2.715*	0.068	4	2.798	0.090	4	2.823	0.112	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8C - Clinical chemistry - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	N
ALKALINE PHOSPHATASE U/l	42	(n)	169.54	30.37	4	171.51	44.14	4	199.58	23.49	4	262.89	119.73	4
ALANINE TRANSFERASE U/l	42		19.84	5.34	4	21.15	1.96	4	25.49	7.62	4	25.27	10.44	4
ASPARTATE TRANSFERASE U/l	42	(n)	11.07	0.97	4	11.92	1.62	4	15.18	6.58	4	12.83	1.60	4
UREA mg/dl	42	(n)	26.39	2.87	4	26.03	2.44	4	27.88	0.46	4	34.40	9.11	4
GLUCOSE mg/dl	42		97.64	7.77	4	100.87	2.39	4	94.16	1.81	4	96.71	7.77	4
TOTAL BILIRUBIN mg/dl	42		0.0850	0.0129	4	0.0850	0.0058	4	0.0700	0.0294	4	0.0950	0.0173	4
TOTAL CHOLESTEROL mg/dl	42		156.14	15.96	4	152.20	20.66	4	170.49	20.40	4	157.10	11.97	4
CREATININE mg/dl	42		0.72	0.07	4	0.83	0.06	4	0.83	0.08	4	0.92*	0.12	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8C - Clinical chemistry - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
TOTAL PROTEIN g/dl	42	5.72	0.18	4	5.74	0.39	4	6.05	0.49	4	5.91	0.17	4
ALBUMIN %	42	66.90	1.05	4	64.98	1.45	4	63.60	3.63	4	66.65	1.96	4
ALPHA 1 GLOBULIN %	42	4.08	0.33	4	4.25	0.24	4	4.60*	0.14	4	4.05	0.24	4
ALPHA 2 GLOBULIN %	42	6.20	0.50	4	6.30	0.43	4	6.43	1.26	4	7.05	0.79	4
BETA GLOBULIN %	42	8.32	0.65	4	10.95*	1.62	4	9.48	1.76	4	7.73	0.96	4
GAMMA GLOBULIN %	42	14.53	0.87	4	13.53	1.55	4	15.95	2.03	4	14.53	0.69	4
ALBUMIN/GLOBULIN RATIO	42	2.023	0.095	4	1.863	0.121	4	1.768	0.278	4	2.008	0.176	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8C - Clinical chemistry - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
CHLORIDE mmol/l	42	107.21	2.92	4	106.64	2.75	4	105.17	5.30	4	103.33	3.67	4
SODIUM mmol/l	42	146.125	1.686	4	145.700	1.014	4	146.100	2.245	4	147.200	1.103	4
POTASSIUM mmol/l	42	4.878	0.313	4	4.975	0.172	4	5.070	0.638	4	4.847	0.152	4
CALCIUM mmol/l	42	2.710	0.099	4	2.698	0.024	4	2.668	0.122	4	2.680	0.049	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8C - Clinical chemistry - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ALKALINE PHOSPHATASE U/l	42	161.90	34.23	4	176.07	38.39	4	175.36	60.97	4	149.90	29.32	4
ALANINE TRANSFERASE U/l	42	19.81	7.01	4	18.20	2.72	4	20.00	4.20	4	17.50	2.59	4
ASPARTATE TRANSFERASE U/l	42	9.91	1.71	4	12.41	2.13	4	13.94*	1.48	4	12.19	0.79	4
UREA mg/dl	42	28.01	4.93	4	29.32	6.13	4	36.76	5.72	4	31.22	4.56	4
GLUCOSE mg/dl	42	93.56	3.18	4	93.71	7.28	4	93.86	3.86	4	89.73	2.18	4
TOTAL BILIRUBIN mg/dl	42	0.1000	0.0245	4	0.0950	0.0129	4	0.0875	0.0096	4	0.1200	0.0141	4
TOTAL CHOLESTEROL mg/dl	42	187.79	35.50	4	133.12**	17.69	4	141.08*	10.65	4	143.74*	9.26	4
CREATININE mg/dl	42	0.79	0.08	4	0.71	0.04	4	0.81	0.12	4	0.83	0.07	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8C - Clinical chemistry - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
TOTAL PROTEIN g/dl	42	5.87	0.16	4	5.57	0.31	4	5.83	0.09	4	5.99	0.19	4
ALBUMIN %	42	67.33	1.78	4	67.55	1.75	4	66.25	3.35	4	66.95	1.97	4
ALPHA 1 GLOBULIN %	42	4.10	0.50	4	4.58	0.31	4	4.40	0.22	4	4.33	0.15	4
ALPHA 2 GLOBULIN %	42	6.47	1.95	4	5.40	1.07	4	5.68	0.52	4	5.58	0.78	4
BETA GLOBULIN %	42	7.35	0.99	4	8.10	0.98	4	7.93	1.63	4	7.20	0.57	4
GAMMA GLOBULIN %	42	14.75	1.17	4	14.48	1.86	4	15.75	1.46	4	15.98	1.24	4
ALBUMIN/GLOBULIN RATIO	42	2.065	0.166	4	2.088	0.168	4	1.985	0.294	4	2.035	0.184	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8C - Clinical chemistry - Week 6 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day	Control Mean	Control SD	N	Group 2 Mean	Group 2 SD	N	Group 3 Mean	Group 3 SD	N	Group 4 Mean	Group 4 SD	N
CHLORIDE mmol/l	42	105.24	2.04	4	103.93	2.54	4	103.69	1.52	4	102.92	1.06	4
SODIUM mmol/l	42	147.600	0.986	4	144.775**	1.146	4	144.225**	1.243	4	144.825**	0.659	4
POTASSIUM mmol/l	42	4.843	0.272	4	4.183	0.407	4	4.405	0.169	4	4.685	0.487	4
CALCIUM mmol/l	42	2.653	0.067	4	2.678	0.076	4	2.763	0.079	4	2.713	0.057	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8D - Clinical chemistry - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
ALKALINE PHOSPHATASE U/l	86	(n)	136.07	27.79	4	137.68	35.48	4	167.35	16.39	4	199.96	96.95	4
ALANINE TRANSFERASE U/l	86	(n)	23.62	6.82	4	21.28	1.22	4	22.84	2.42	4	25.52	10.88	4
ASPARTATE TRANSFERASE U/l	86		13.18	0.97	4	11.65	1.22	4	12.83	1.13	4	13.59	2.02	4
UREA mg/dl	86		28.88	4.38	4	28.15	4.52	4	26.98	2.25	4	32.10	4.44	4
GLUCOSE mg/dl	86	(n)	96.36	3.45	4	99.84	1.10	4	101.48	3.38	4	97.65	9.53	4
TOTAL BILIRUBIN mg/dl	86		0.1075	0.0171	4	0.1175	0.0171	4	0.1375	0.0330	4	0.1250	0.0100	4
TOTAL CHOLESTEROL mg/dl	86		132.35	8.77	4	141.29	14.60	4	153.71	12.02	4	137.11	15.14	4
CREATININE mg/dl	86	(n)	0.69	0.07	4	0.74	0.10	4	0.76	0.01	4	0.80	0.06	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8D - Clinical chemistry - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day		Control Mean	SD	N	Group 2 Mean	SD	N	Group 3 Mean	SD	N	Group 4 Mean	SD	I
TOTAL PROTEIN g/dl	86		5.44	0.15	4	5.50	0.31	4	5.76	0.32	4	5.56	0.12	4
ALBUMIN %	86		66.45	0.84	4	65.05	2.12	4	63.48	2.74	4	66.20	1.92	4
ALPHA 1 GLOBULIN %	86		4.03	0.31	4	4.23	0.21	4	4.38	0.33	4	4.23	0.26	4
ALPHA 2 GLOBULIN %	86		6.35	0.54	4	6.50	0.52	4	6.40	0.71	4	6.98	0.62	4
BETA GLOBULIN %	86	(n)	8.43	0.13	4	11.60	2.15	4	9.95	1.38	4	8.25	0.89	4
GAMMA GLOBULIN %	86		14.73	0.59	4	12.65	1.65	4	15.80	1.94	4	14.38	0.71	4
ALBUMIN/GLOBULIN RATIO	86		1.983	0.076	4	1.868	0.181	4	1.750	0.194	4	1.965	0.169	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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(Dr. Alfredo Nunziata)

FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8D - Clinical chemistry - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

MALES

Parameter/units	Study Day	Control Mean	Control SD	Control N	Group 2 Mean	Group 2 SD	Group 2 N	Group 3 Mean	Group 3 SD	Group 3 N	Group 4 Mean	Group 4 SD	Group 4 N
CHLORIDE mmol/l	86	98.83	3.67	4	99.21	1.05	4	97.24	3.58	4	97.89	1.07	4
SODIUM mmol/l	86	142.875	1.248	4	142.775	0.315	4	142.625	0.900	4	143.225	1.036	4
POTASSIUM mmol/l	86	4.660	0.283	4	4.758	0.160	4	4.727	0.221	4	4.693	0.117	4
CALCIUM mmol/l	86	2.565	0.107	4	2.640	0.032	4	2.620	0.062	4	2.598	0.045	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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FDP: 13 WEEK INTRAVENOUS TOXICITY STUDY IN DOGS

TABLE 8D - Clinical chemistry - Week 13 of treatment - Mean data

STUDY NO.: 235-003-009

FEMALES

Parameter/units	Study Day		Control Mean	Control SD	N	Group 2 Mean	Group 2 SD	N	Group 3 Mean	Group 3 SD	N	Group 4 Mean	Group 4 SD	N
ALKALINE PHOSPHATASE U/l	86		121.79	23.02	4	125.19	19.35	4	130.44	50.51	4	119.39	21.61	4
ALANINE TRANSFERASE U/l	86		18.00	5.08	4	20.09	4.48	4	20.46	5.22	4	18.23	2.95	4
ASPARTATE TRANSFERASE U/l	86		11.24	1.26	4	14.43	3.22	4	13.47	1.71	4	12.05	1.82	4
UREA mg/dl	86		27.58	6.28	4	29.83	2.45	4	35.48	6.64	4	26.98	5.38	4
GLUCOSE mg/dl	86		96.09	4.71	4	95.61	7.00	4	95.67	8.95	4	96.64	4.71	4
TOTAL BILIRUBIN mg/dl	86	(n)	0.1375	0.0550	4	0.1450	0.0100	4	0.1625	0.0250	4	0.1825	0.0096	4
TOTAL CHOLESTEROL mg/dl	86		157.47	26.87	4	123.45	9.66	4	128.95	20.18	4	130.57	8.94	4
CREATININE mg/dl	86		0.73	0.08	4	0.76	0.06	4	0.87	0.10	4	0.81	0.08	4

Controls from group(s): 1
Data homogeneous by Bartlett's Test — Test of significance is Dunnett's Test
(n) Data nonhomogeneous by Bartlett's Test — Modified t test of significance
* Indicates group mean is significantly different from control at level P = .05
** Indicates group mean is significantly different from control at level P = .01

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